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Statistical Issues in Carcinogenic Risk Assessment

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Considerable progress has been made on the development of a variety of analytical methods to aid in the carcinogenic risk associated with exposure to both occupational and environmental agents. Although the development of these methods has been accompanied by consideration of many statistical issues, there are many areas where additional effort could be directed if these analytical methods are to provide the most appropriate interpretation of risk. These issues include methods of combining multiple studies to obtain an overall risk estimate, the robustness of the statistical model, methods of selection among competing models, an assessment of the effect of different measures of exposure on the estimated dose-response relationship, and development of surveillance methodology. These issues are discussed, and productive areas of future research are indicated.

Introduction

The term "risk assessment" is used in a variety of ways. Each of the areas of risk ascertainment covered in this conference has statistical issues specific to the methodology being used to ascertain risk. Because of the breadth of the area, this paper is restricted to the outcome of cancer as the potential risk from exposure and focuses on problems related to epidemiological studies and does not address the many issues related to incorporating animal studies into risk assessment. In a further attempt to make the scope of this topic more specific, risk assessment is characterized as trying to answer one of the following three questions: Does an excess risk exist from cancer in the presence of a specified exposure? Is there a dose-response relationship of exposure and risk? Can we estimate the effect of controlling exposure?

If the usefulness of present models of carcinogenic risk assessment are to be improved, several statistical issues need to be addressed. These topics relate to the following five general areas: *a*) combining data across different studies; *b*) model robustness; *c*) model discrimination; *d*) measurement of exposure; and *e*) problems of screening and surveillance. This paper discusses each of these general areas as they relate to the three general questions posed about risk assessment.

Methods of Combining Data across Studies

The methodology of determining whether there is a risk from exposure to a potential carcinogen has been well developed in recent years. There are numerous papers that have addressed methodology to assess risk for both case-control studies and cohort studies, and these methodologies incorporate adjustments for potential confounders (*1*–*5*). However, in deciding whether an exposure results in an increase in risk, one is often faced with synthesizing information from multiple studies, which in some cases appear to have conflicting results. Part of the reason for the appearance of conflicting conclusions relates to the oversimplistic but widely used practice of interpreting statistically significant results (usually $p \leq 0.05$) as a positive study and declaring results where $p > 0.05$ a negative study. Such a practice ignores the concept of statistical power in hypotheses testing as well as the elevated type I error in studies where there are multiple hypotheses.

Power is the probability of detecting a true risk when one exists and is a function of the magnitude of the true risk and the sample size. Often studies do not have sufficient sample size to detect a moderate risk. For example, in a negative study of 518 workers exposed to trichloroethylene (*6*), Rockette (*7*) calculated a power of 0.81 associated with 3-fold risk of lung cancer and of 0.61 associated with a 2-fold risk.

Even large studies may have low power if the risk estimate is restricted to a highly exposed subgroup with long-term exposure. For example, Rockette and Arena report power of 0.92 of detecting a 25% increase in lung cancer of workers in the potroom or carbon department of aluminum reduction plants (*8*). However, one of the higher exposures of coal tar volatiles occurs for anode men in the Soderberg process. The power of detecting a 100% increase in lung cancer for men employed at least 20 years in this job and process is 0.32.

Although low power may result in failing to detect a carcinogenic risk for a specific study, multiple tests of hypotheses within a study may result in falsely declaring risk. The probability of falsely rejecting at least one of multiple hypotheses is called the experimentwise error rate and is seldom addressed in epidemiological studies. Rockette and Arena (*9*) demonstrate that using a standard battery of 24 categories of malignancy in two standardized computer programs (*10,11*) often used in the analysis of mortality data from occupational cohorts led to an experimentwise error rate of 0.36, not the 0.05 associated with each individual comparison.

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If we are to adequately synthesize data from multiple studies, the two concepts of power and multiple comparisons must be appropriately addressed. The practice of combining results from multiple studies is often called meta analysis. Meta analysis is not a new concept and has been widely used in the educational research and social science areas (*12–15*) and more recently in the health area (*16–20*). However, in the medical and health science areas, most of the applications have been to synthesize results from well-controlled studies (usually randomized trials), and the more difficult application to epidemiological studies has received less attention.

Some general issues related to meta analysis in epidemiological studies have been discussed in several papers (*21–24*), and more recently, methods of meta analysis been applied to occupational data. Synthesis of data across studies to assess cancer risks has been conducted for workers exposed to vinyl chloride (*25*), lead (*26*), asbestos (*27*), benzene (*28*), and aluminum workers (*29*). In the more general area of environmental exposure, the effect of passive smoking on lung cancer has been evaluated using a meta analysis (*30*). Given the rapid proliferation of meta analyses in related medical areas, it is likely that there will be an increasing use in occupational and environmental risk assessment. However, the application of meta analysis to the medical area, even when restricted to randomized trials, has its limitations (*31–34*), and in the area of environmental epidemiology additional problems occur.

Epidemiological studies have a greater variability of design. Some studies are case-control studies, and there are a variety of options for selecting the control group. The proportionate mortality study is an approach used in a substantial number of occupational mortality studies. Using only deaths known to the employer, the proportion of deaths from a specific cause within the group of all causes is compared to the proportion within a control group. The cohort study obtains risk estimates over a designated observation period and may have either an internal or external control. The estimates of risk obtained in these various types of studies, although related, are not mathematically the same. Furthermore, different control groups and differing information on potential confounders may lead to substantially different biases in the risk estimate. Greenland (*23*) has described procedures to adjust for confounding when combining data across epidemiological studies, but the methods are approximate and highly dependent on assumptions that cannot be confirmed with the amount of information usually available in a published report.

Statistical Models

The second general question posed in regard to risk assessment relates to ascertaining a dose-response relationship. The determination of a dose-response curve is closely related to the other two general questions on risk we posed earlier. First, existence of a dose-response relationship provides further confirmation of the existence of risk because it is one of the epidemiological criteria often specified for a cause-effect relationship (*35*). Secondly, if the dose-response curve is ascertained, it provides useful information to estimate the effect of limiting exposure. Both purposes require the specification of a statistical model.

A statistical model may be used to provide a context in which to test hypotheses, to provide insight into biological mechanisms, or to provide information outside the range of the data. The robustness of the model may depend upon the purpose for which it is used. It is likely that if one is simply trying to ascertain whether risk increases with dose and the exact form of the dose response is not specified, then the model may still be robust with respect to identifying a monotonic relationship. However, it should be recognized that a good fit of the model to the data set is a necessary but not sufficient condition for establishing the appropriateness of an explanation of biological mechanisms, and extrapolation outside the range of the data is often a procedure that may result in poor estimates if the model is incorrectly specified.

In attempting to ascertain risk from exposures believed to be carcinogenic, a variety of models have been proposed from which inferences relative to magnitude of the risk, biological mechanisms, and extrapolation to low doses may be based. The goal of this paper is not to review in detail various cancer models. Interested readers may consult reviews by Whittemore and Keller (*36*); Armitage (*37*); the work of Moolgavkar and colleagues (*38–40*), and a nonmathematical summary of the various competing models by Chu (*41*).

Armitage (*37*) discusses three general classes of models which he feels are the main contenders for generally applicable theories. The multistage model and its modifications (*42–45*) is based on the assumption that a cell becomes malignant only after going through k transitions. As the model has developed, the transition rates between successive stages are not required to be equal, and at least one of the stages is assumed to be linearly related to dose. Thus, the ith dose-related transition rate is assumed to be equal to a background transition rate plus the product of a constant, b_i and the instantaneous dose rate at time t. The constant b_i is called the potency parameter and represents the increase in the transition rate per unit increase in dose. This model is often criticized for not having a biological basis since more than two transition stages of cancer cells has not been demonstrated experimentally.

The two-stage model proposed by Moolgavkar and Knudson (*38*) is often assumed to have more of a biological basis. It is formulated biologically in terms of cell divisions, and statistically it is formulated as a birth-death process. This model views carcinogenesis as the end result of a two-stage, irreversible process. It assumes that malignant tumors arise from a single malignant progenitor cell and that the transformation of susceptible stem cells to malignancy is independent of the transformation of other stem cells. The model incorporates mutation rates that summarize the likelihood that during cell division a normal cell will result in an intermediate cell and a second mutation rate summarizing the likelihood that an intermediate cell will result in a malignant cell during division.

The third class of models considers only the time till presentation of the tumor and does not include the more detailed mathematical concepts of mutation rates and growth rates of intermediate cells that are part of the multistage or Moolgavkar and Knudson model. This type of procedure was proposed in earlier papers by Pike (*46*) and Peto and Lee (*47*) where time until occurrence of tumor in mice exposed to a constant dose of a carcinogen was assumed to be a Weibull distribution. The

occurrence of tumor was hypothesized as occurring when the first of a large number of potentially malignant cells culminates in a clinically detectable tumor. The distribution of time until occurrence of tumor can be viewed as the distribution of the minimum time to event of a large number of independent, identically distributed random variables representing the times until occurrence of tumor from an individual cell. The Weibull distribution was selected because it is one of the limiting extreme value distributions for the minimum-order statistic. This approach of modeling time until occurrence of tumor was recently applied (*48*) to incidence data for breast, ovary, and endometrium cancers and resulted in a reasonably good fit of the data.

One advantage of having the correctly specified model is that it enables one to draw inferences outside of the range of the data as well as make useful decisions of the benefit of change in exposure. For the multistage model, Day and Brown (*49*) summarize the impact of the specific stage affected by the carcinogen on the observed benefit when the exposure is eliminated. If dose affects the transition rate for an early stage, it takes longer to observe the effect of reduced exposure to the carcinogen than if a later stage is affected.

There is work that could be done in adapting these models to more complicated situations. For example, recent work has focused on generalizing these models from the requirement of a single measure of dose to models where the dose may vary over time (*40,50*). Another possible extension would be incorporating benign tumors as a third stage of disease. Formal introductions of the concepts of competing risk and random effects would also be useful generalizations. However, our focus is not to indicate what specific modifications might be made to existing statistical models but to address some statistical issues of a more general nature that should be explored if such models are to be more usefully employed.

Model Robustness

More work needs to be done to determine the robustness of a given model relative to the inferences being made. Three specific questions of importance are as follows: How robust is the estimate of the potency parameter? How robust is the model when extrapolating to low dose? How robust is the method of assessing the effect of controlling exposure?

In the two-stage, dose-related, multistage model, it has been demonstrated that the confidence interval estimates of the potency parameter based on Wald's statistic are not well behaved for extreme parameter values but that the standard methods of placing confidence intervals have good coverage and power properties for a single-stage, dose-related, multistage model (*51*). There has been considerable work as well as debate on extrapolation of high-dose results to estimate a low-dose effect (*52*). Even within a single family of models, there can be considerable difference in estimates depending on the values of the parameter. Although the standard statistical approach to summarize such variability is a confidence interval estimate, Crump and Howe (*53*) note that the absence of regularity conditions sufficient for applying standard methods and the inappropriateness often-applied asymptotic results to low-dose extrapolation has resulted in additional controversy. Thomas (*54*) demonstrated in a simulation study that the estimate of stage at which the carcinogen acted in a multistage model assuming a constant intensity of exposure over time was robust with respect to error in the measurement of intensity. Such an observation is important when attempting to estimate the effects of removing an exposure from the general population. These results represent a beginning in regard to investigating various aspects of robustness, but more work needs to be done.

Unfortunately, in assessing the effect of low exposure to cancer risk, even with further investigations the ability to support the validity of our inference is limited by the inability to obtain estimates of the effect of low exposure from epidemiological studies. The general shape of the dose-response curve at low levels must be formulated based on our knowledge of the mechanisms of the carcinogenic process. Central to the issue of determining low exposure effects is whether a threshold exists, i.e., a level of exposure below which there is no increased risk. Based on the current view of the carcinogenic process, a linear nonthreshold model appears to be the most widely accepted method of estimating risk at low exposure (*55*). The linear nonthreshold model has been described within the context of a modified multistage model by Crump (*56*). The assumptions implicit in a model relative to the behavior of the dose-response curve at low exposure may have a substantial effect on low-dose risk estimates. However, in the absence of sufficient empirical observations, model selection at low dose must be made based on perceived biological mechanisms rather than statistical considerations.

Model Discrimination

Another statistical issue relates to model discrimination. We have noted that several models may fit the same database, but the models may have different underlying biological assumptions. An integral part of the selection of a model entails using available biological data to evaluate the assumptions made in the various models. Recently, Bogen (*57*) has concluded that available biological evidence does not support the assumption of exponential growth of precancerous cells, which is one of the assumptions of most of the multistage cancer risk models, including the two-stage model of Moolgavkar and Knudson. Bogen suggests changes to existing models that he believes may correct for underestimates of small increments of cancer risk that would result if exponential growth is assumed (*57*). This continued scrutiny of the biological assumptions is desirable and will probably continue. However, it is likely that all of the statistical models posed will continue to be considered simplistic when evaluated by a cell biologist in regard to explaining the complicated process of carcinogenesis.

In conjunction with assessing the underlying biological assumptions, more work could be done in determining which of the existing models best fits various data sets. It is likely that if model discrimination was conducted in a hypothesis testing format, it might lead to some recognition of the limitations of some of the models, which might then lead to eventual improvement. There should be systematic application of competing models to a large number of epidemiological studies. Ideally, one might develop a formal statistical procedure to discriminate competing models, and then with existing data sets, formally test which model best fits the data. Simulation studies could be used to supplement such analysis to evaluate the power of discrimination among the various studies.

Testing which of two specific models in a general class of models is most appropriate has been applied to select between additive and multiplicative models (*58–59*). The classical likelihood ratio test is a well-accepted approach and has been applied to situations where the two competing models are special cases of a more general class of models. However, it is not generally recognized that likelihood ratio procedures have also been applied to situations in which the two models being compared are not members of the same family. For example, Dumonceaux and Antle (*60*) have provided a test of lognormal versus the Weibull distribution using likelihood ratio procedures. Statistical procedures to compare competing models in carcinogenic risk assessment would be more complicated, but development of even an approximate method to formally discriminate among competing models would be a useful procedure.

Exposure Data

One of the areas that continues to be a concern is the accuracy of exposure data and the most appropriate way to summarize it for purposes of risk assessment. The individual measurements used for exposure in most risk assessment studies are themselves an average of values for a group of individuals. Little work has been done to assess how using such averages in these models would compare to using each individual's sample. A first step in this regard would be considering dose as a random effect instead of the fixed effect that is assumed in most carcinogenic models. Similarly, more investigation is needed to determine the sensitivity of the inferences made from the various models to different methods of characterizing dose (average exposure, maximum exposure, cumulative exposure, etc.)

Screening and Early Detection of Risk

One of the objectives of public health is early detection of health problems. Many of the epidemiologic studies to assess carcinogenic risk are conducted after large numbers of workers have already been exposed. Although the requirements of a sufficiently large population to obtain acceptable statistical power and the existence of a latency period for many diseases make it more likely that larger numbers of individuals will be exposed by the time a risk has been detected, there has been little effort to apply the existing statistical methods of sequential analysis to detect risk earlier. Adopting such models would require modifications to incorporate the concept of disease latency and appropriate control of type I error if multiple diseases are being screened. Knowledge of specific factors that relate to risk of disease may suggest evaluating certain subsets of workers or including data on potential confounders so that statistical power may be increased. If such surveillance designs are developed, they could be applied to new processes that are believed to have the potential for an elevated cancer risk.

Summary

Continued work is needed in comparing the biological justification of different models, testing models on epidemiological populations, and evaluating model robustness. Little work has been done to develop better meta analysis for assessing risk across epidemiological studies, to develop methods to test the applicability of competing models, to evaluate various strategies of early identification of toxic substances, or to evaluate the impact on the estimate of risk of differing ways of measuring exposure. It needs to be emphasized that the use of models in an area such as this has to be done cautiously and that any statistical model will probably be oversimplistic biologically. Nevertheless, such models help us organize our thinking about carcinogenesis and suggest new hypotheses to be tested. However, we must avoid the temptation of overinterpretation of the results obtained when fitting a model; in this regard we need more rigorous applications of the models to large numbers of databases, more simulation studies to determine how sensitive the conclusions are to model inadequacy, and more statistical theory to enable comparisons among the different competing models.

In closing, the area of development of models for carcinogenic risk assessment should be viewed as many other developing areas. It is unlikely that the models we are currently using to describe the mechanisms of cancer will be the ones we would select 10 years from now. Nevertheless, recognizing these limitations does not imply that we discard all the present approaches. The following quotation from Nemath would appear particularly appropriate in the area of risk assessment: "Scientists are like Sailors trying to rebuild a ship on the open sea. In the end, every plank may be changed, but at any stage there are planks we leave alone."

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REFERENCES

1. Breslow, N. Some statistical models useful in the study of occupational mortality. In: Environmental Health: Quantitative Methods (A. Whittemore, Ed.), Proceedings of a Conference sponsored by SIAM Institute of Mathematics and Society and supported by the National Science Foundation of Alta, UT, July 5–9, 1976. pp. 88–103.
2. Pasternack, B. S., and Shore, R. E. Statistical methods for assessing risk following exposure to environmental carcinogens. In: Environmental Health: Quantitative Methods (A. Whittemore, Ed.), Proceedings of a Conference sponsored by SIAM Institute of Mathematics and Society and supported by the National Science Foundation of Alta, UT, July 5–9, 1976. pp. 49–69.
3. Breslow, N. E., Lubin, J. H., Marek, P., and Langholz, B. Multiplicative models and cohort analysis. J. Am. Stat. Assoc. 78(381): 1-12 (1983).
4. Gilbert, E. S. The assessment of risks form occupational exposures to ionizing radiation. In: Environmental Health: Quantitative Methods (A. Whittemore, Ed.), Proceedings of a Conference sponsored by SIAM Institute of Mathematics and Society and supported by the National Science Foundation at Alta, UT, July 5–9, 1976, pp. 209–225.
5. Breslow, N. E. Analysis of survival data under the proportional hazards model. Int. Stat. Rev. 43: 45–58 (1978).
6. Axelson, O., Anderson, K., Hogstedt, C., Holmberg, B., Molina, G., and de Verdier, A. A cohort study on trichloroethylene response and cancer mortality. J. Occup. Med. 20: 194 (1978).
7. Rockette, H. E. Occupational biostatistics. In: Environmental and Occupational Medicine (W. N. Rom, A. D. Renzetti, J. S. Lee, and V. E. Archer, Eds.), Little, Brown and Company, Boston, 1981, pp. 35–41.
8. Rockette, H. E., and Arena, V. C. Mortality studies of aluminum reduction plant workers: potroom and carbon department. J. Occup. Med. 25(7): 549–557 (1983).
9. Rockette, H. E., and Arena, V. C. Evaluation of the proportionate mortality index in the presence of multiple comparisons. Stat. Med. 6: 71-77 (1987).
10. Marsh, G. M., and Preininger, M. OCMAP: a user-oriented occupational cohort mortality analysis program. Am. Stat. 34: 245–246 (1980).

11. Monson, R. R. Analysis of relative survival and proportional mortality. Comput. Biomed. Res. 7: 325–332 (1974).
12. Light, R. J., and Pillemer, D. B. Reviewing Research: The Science of Summing Up. Harvard University Press, Cambridge, MA, 1984.
13. Hunter, J. E., Schmidt, F. L., and Jackson, G. B. Meta-Analysis: Cumulating Research Findings across Studies, Vol. 4. Sage Publications, Beverly Hills, CA, 1982.
14. Glass, G. V., McGaw, B., and Smith, M. L. Meta-Analysis in Social Research. Sage Publications, Beverly Hills, CA, 1981.
15. Hedges, L. V., and Olkin, I. Statistical Methodology for Meta-Analysis. Academic Press, New York, 1984.
16. Collins, R., and Langman, M. Treatment with histamine-H antagonists in acute upper gastrointestinal hemorrhage. N. Engl. J. Med. 313: 659–666 (1985).
17. Collins, R., Yusuf, S., and Peto, R. Overview of randomized trials of diuretics in pregnancy. Br. Med. J. 290: 17–22 (1986).
18. Tran, Z. V., and Weltman, A. Differential effects of exercise on serum lipid and lipoprotein levels seen with changes in body weight: a meta analysis. J. Am. Med. Assoc. 254: 919–924 (1985).
19. Himel, H. N., Liberati, A. L., Gelber, R. D., and Chalmers, T. C. Adjuvant chemotherapy for breast cancer: a pooled estimate based on published randomized control trials. J. Am. Med. Assoc. 256: 1148–1159 (1986).
20. Early Breast Cancer Trialists' Collaborative Group. Effects of adjuvant tamoxifen and cytotoxic therapy on mortality in early breast cancer: an overview of 61 randomized trials among 28,896 women. N. Engl. J. Med. 319: 1681–1692 (1988).
21. Dinman, B. D., and Sussman, N. B. Uncertainty, risk, and the role of epidemiology in public policy development. J. Occup. Med. 27(7): 511–516 (1983).
22. Louis, T. A., Fineberg, H. V., and Mosteller, R. Findings for public health for meta-analysis. Annu. Rev. Public Health 6: 1–20 (1985).
23. Greenland, S. Quantitative methods in the review of epidemiologic literature. Epidemiol. Rev. 9: 1–30 (1987).
24. Jenick, M. Meta-analysis in medicine: where we are and where we want to go. J. Clin. Epidemiol. 42(1): 35–44 (1989).
25. Beaumont, J. J., and Breslow, N. E. Power considerations in epidemiologic studies of vinyl chloride workers. Am. J. Epidemiol. 114: 725–734 (1981).
26. Steinberg, E. P., and Shepard, D. S. Lead—is it carcinogenic? Public Health Rev. 11(2): 177–192 (1983).
27. Frumkin, H., and Berlin, J. Asbestos exposure and gastrointestinal malignancy review and meta-analysis. Am. J. Ind. Med. 14: 79–95 (1988).
28. Austin, H., Delzell, E., and Cole, P. Benzene and leukemia: a review of the literature and a risk assessment. Am. J. Epidemiol. 127(3): 419–439 (1988).
29. Abramson, M. J., Wlodarczyk, J. H., Saunders, N. A., and Hensley, M. J. Does aluminum smelting cause lung disease? Am. Rev. Respir. Dis. 139: 1042–1057 (1989).
30. National Research Council. Environmental Tobacco Smoke: Measuring Exposures and Assessing Health Effects. National Academy Press, Washington, DC, 1986.
31. Rockette, H. E., and Redmond, C. K. Limitations and Advantages of Meta-Analysis in Clinical Trials. Recent Results in Cancer Research, Vol. III. Springer-Verlag, Berlin, 1988.
32. DerSimonian, R., and Laird, N. Meta-analysis in clinical trials. Controlled Clin. Trials 7: 177–188 (1986).
33. Gelber, R. D., and Goldhirsch, A. The concept of an overview of cancer clinical trials with special emphasis on early breast cancer. J. Clin. Oncol. 4(11): 1696–1703 (1986).
34. Redmond, C. K., and Rockette, H. E. Meta-analysis: considerations of its worth and its limitations. In: Adjuvant Therapy of Cancer, Vol. 5 (S. E. Salmon, Ed.), Grune and Stratton, New York, 1987, pp. 467–478.
35. Schlsselman, J. J. Case-Control Studies Design, Conduct, Analysis. Oxford University Press, New York, 1982.
36. Whittemore, A., and Keller, J. B. Quantitative theories of carcinogenesis. SIAM Rev. 20(1): 1–30 (1978).
37. Armitage, P. Multistage models of carcinogenesis. Environ. Health Perspect. 63: 195–201 (1985).
38. Moolgavkar, S. H., and Knudson, A. G. Mutation and cancer: a model for human carcinogenesis. J. Natl. Cancer Inst. 66(6): 1037–1051 (1981).
39. Moolgavkar, S. H., Day, N. E. and Stevens, R. G. Two-stage model for carcinogenesis: epidemiology of breast cancer in females. J. Natl. Cancer Inst. 65(3): 559–569 (1980).
40. Moolgavkar, S. H., Dewanji, A., and Venzon, D. J. A stochastic two-stage model for cancer risk assessment. I. The hazard function and the probability of tumor. Risk Anal. 8(3): 383–392 (1988).
41. Chu, K. C. Biomathematical models for cancer: a nonmathematical view of mathematical models for cancer. J. Chron. Dis. 40(Suppl. 2): 1635–1705 (1987).
42. Stocks, P. A study for the age for cancer of the stomach in connection with a theory of the cancer producing mechanism. Br. J. Cancer 7: 407–417 (1953).
43. Nordling, C. O. A new theory in the cancer-inducing mechanism. Br. J. Cancer 7: 68–72 (1953).
44. Armitage, P., and Doll, R. The age distribution of cancer and a multistage theory of carcinogenesis. Br. J. Cancer 8: 1–12 (1954).
45. Whittemore, A. Quantitative theories of carcinogenesis. Adv. Cancer Res. 27: 55–58 (1978).
46. Pike, M. C. A method of analysis of a certain class of experiments in carcinogenesis. Biometrics 22: 142–161 (1966).
47. Peto, R., Roe, F. J. C., Lee, P. N., Levy, L., and Clack, J. Cancer and aging in mice and men. Br. J. Cancer 32: 411–426 (1975).
48. Pike, M. C. Age-related factors in cancers of the breast, ovary and endometrium. J. Chron. Dis. 40(suppl. 2): 59–69 (1987).
49. Day, N. E., and Brown, C. C. Multistage models and primary prevention of cancer. J. Natl. Cancer Inst. 64(4): 977–989 (1980).
50. Crump, K. S., and Howe, R. B. The multistage model with a time-dependent dose pattern: applications to carcinogenic risk assessment. Risk Anal. 4(3): 163–176 (1984).
51. Patwardhan, R. N. Inferential Procedures for Multistage Models for Carcinogenic Risk Assessment with Applications. Ph.D. Dissertation, University of Pittsburgh, Pittsburgh, PA, 1989.
52. Krewski, D., Murdoch, D., and De Wanji, A. Statistical modeling and extrapolation of carcinogenesis data. In: Modern Statistical Methods in Chronic Disease Epidemiology (S. H. Moolgavkar and R. L. Prentice, Eds.), John Wiley and Sons, New York, 1986, pp. 259–282.
53. Crump, K. S., and Howe, R. B. A review of methods for calculating statistical confidence limits in low dose extrapolation. In: Toxicological Risk Assessment, Vol. 1: Biological and Statistical Criteria (D. B. Clayson, D. Krewski, and I. Munro, Eds.), CRC Press, Boca Raton, FL, 1985, pp. 187–203.
54. Thomas, D. C. Use of computer simulation to explore analytical issues in nested case-control studies of cancer involving extended exposures: methods and preliminary findings. J. Chron. Dis. 40(suppl 2): 201–208 (1987).
55. Anderson, E. L. Quantitative approaches in use to assess cancer risk. Risk Anal. 3(4): 277–295 (1983).
56. Crump, K. S. An improved procedure for low dose carcinogenic risk assessment from animal data. J. Environ. Pathol. Toxicol. 5: 675–684 (1980).
57. Bogen, K. T. Cell proliferation kinetics and multistage cancer risk models. J. Natl. Cancer Inst. 81(4): 267–277 (1989).
58. Thomas, D. C. General relative risk models for survival time and matched case-control analysis. Biometrics 37: 673–686 (1981).
59. Moolgavkar, S. H., and Venzon, D. J. General relative risk regression models for epidemiologic studies. Am. J. Epidemiol. 126(5): 949–961 (1987).
60. Dumonceaux, R., and Antle, C. E. Discrimination between the lognormal and the Weibull distributions. Technometrics 15: 923–926 (1973).